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# CLINICAL AND METABOLIC CONSEQUENCES IN INFANTS OF DIABETIC MOTHERS

**[1]Dr. Kushvanth K. N., [2]Dr. Gurpreet Kaur Dhillon, MD, *[3]Dr. Harpreet Singh Dhillon, MD and [4]Dr. Shibu Sasidharan, MD, DNB, MNAMS**

[1]MD Paediatrics, Department of Paediatrics, Kodagu Institute of Medical Sciences.
[2]Reader, Department of Paediatrics, 166 Military Hospital, Jammu.
[3]Reader, Department of Psychiatry, 166 Military Hospital, Jammu, India.
[4]Asst. Prof. (Anaesthesiology) HOD, Dept. of Anaesthesiology & Critical Care Level III Hospital, Goma.

***Corresponding Author: Dr. Harpreet Singh Dhillon, MD**

Reader, Department of Psychiatry, 166 Military Hospital, Jammu, India.

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## ABSTRACT

**Introduction**: The prevalence of gestational diabetes mellitus (GDM) is on the rise especially in women of Asian ethnicity. GDM carries with it multitude of feto-maternal complications, the management of which is still a challenge in developing countries. **Methods**: This was a hospital based prospective case control study conducted with 100 neonates to compare clinical outcomes and metabolic profiles in neonates of diabetic mothers compared to neonates of non-diabetic mothers over a period of two years. **Results**: The mothers in GDM group had 66% emergency lower segment caesarean section (LSCS) compared to 32% in Non-GDM group (p=0.001). The infants of diabetic mothers (IDM) had statistically significant higher percentage of preterm births, NICU admission, Hyperbilirubinemia, Hypoglycemia and Polycythemia. The anthropometric and cord blood parametres (Haemoglobin, Hematocrit, Platelet, Calcium and Bilirubin) were comparable in both the groups. **Conclusion**: GDM poses significant risks to both mother and neonate, however optimal glycemic control and meticulous monitoring and treatment protocols can reduce the incidence of certain known complications.

**KEYWORDS**: Gestational Diabetes mellitus, Infants of diabetic mothers, Caesarean section, Macrosomia, Case-control study.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is characterized by carbohydrate intolerance with the onset or first recognition during pregnancy.[1] The World Health Organization (WHO) has predicted that between 1995 and 2025, there will be a 35% increase in the worldwide prevalence of diabetes.[2] Moreover, women born in Asian countries and especially of Indian ethnicity display the highest prevalence of Gestational Diabetes Mellitus (GDM).[3]
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GDM poses an increased risk of complications for the mother (especially preeclampsia and caesarean delivery) as well as the neonate. Infants of diabetic mother (IDM) are at higher risk of complications and congenital anomalies like macrosomia, hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia, prematurity, transient tachypnea of newborn, respiratory distress syndrome, birth asphyxia, congenital heart diseases like interventricular septal hypertrophy, transient hypertrophic subaortic stenosis, cardiomyopathy, cleft lip, cleft palate, sacral agenesis, jitteriness, seizures, movement disorder.[4,5]

Suboptimal prenatal care along with poor maternal glycemic control, vasculopathy, infection, & pregnancy induced hypertension are some of the factors held responsible for the poor perinatal outcome.[6] A strong association between congenital anomalies and maternal glycemic control has been documented[7] and studies have shown that strict control of maternal glucose during pregnancy has a favorable perinatal outcome.[8] This provides us with a window of oppurtunity to prevent/reduce the fetal & neonatal morbidity through scrupulous prenatal & intrapartum care.[6] The management of infants of diabetic mothers can be done effectively based on prevention, early recognition and appropriate treatment of these complications. Comprehensive care of pregnant women with diabetes mellitus has been extensively described yet guidelines regarding the care of their infants are less well established. Moreover there are scanty reports on infants born to diabetic mothers in India compared to developed countries.

Hence the present study was conceived to compare multiple clinical outcomes and metabolic profiles of

neonates born to diabetic mothers and non diabetic mothers after matching subjects in both groups in a tertiary care Armed forces hospital. The results are expected to further our knowledge on the subject in a socio-economically homogenous sample from across the country. With not many studies done on Indian diaspora and especially in Armed forces, this research will be useful in recognizing potentially modifiable factors and implementing necessary remedial measure.

## METHODS

This was a hospital based prospective case control study conducted over two years at the Department of Paediatrics in Mumbai. The study was approved by the Institute ethics committee, and a written informed consent was obtained from the parent(s). All consecutive infants born to mothers with Gestational Diabetes and Pregestational (Type 1 and Type 2) diabetes at our tertiary care centre during the study period formed the study group. The control groups had equal number of consecutively born neonates of non diabetic mothers during the same period. Subjects in the control group were matched with those in the study group for confounding maternal as well as neonatal factors like maternal age, maternal morbidity other than diabetes, period of gestation, mode of delivery and sex of the neonate.

Sample size was calculated using the formula:n= $[z^2p(1-p)]/d^2$, [where:n= sample size, Z = table value of alpha error from standard normal distribution table (0.95), power (p) = 80%, precision error of estimation (d) = 5.5%]. The sample size was claulated, n= [0.95 x 0.95 x 0.8 (0.2)] / 0.055 x 0.055 = 47.7. Hence, each group was allocated 50 consecutively born neonates of diabetic mothers and 50 consecutive neonates born to non-diabetic mothers.

All subjects in both groups were evaluated for birth weight, length, occipitofrontal circumference, clinically detectable congenital anomalies and followed up for neonatal morbidities like hypoglycemia, hyperbilirubinemia and polycythemia. Cord blood samples of both groups were evaluated for serum bilirubin, haemoglobin, haematocrit, calcium, platelet counts and blood sugar levels.

Blood sugar levels were done under aseptic condition. Blood samples were obtained from the heel of foot from neonates of GDM mothers by prick method and checked on glucometer at 1, 2, 3, 6, 12, 24 hours of age as a routine in nursery for neonates of GDM mothers. Neonates of non GDM mothers were monitored for feed adequacy and if symptomatic, underwent glucose tests by glucometer as per hospital protocol. All neonates were monitored clinically for polycythemia and jaundice and evaluated and managed appropriately.

The data were tabulated using Microsoft Excel software and analyzed using Statistical software, SPSS version 20. Level of significance was taken at a 'p' value less than or equal to 0.05. The Chi square statistic was used for testing relationships on categorical variables. Student t-test was used to compare the means of a normally distributed interval dependent variable for two independent groups. The Fisher's exact test was used instead of Chi-square test, when one or more cells had an expected frequency of five or less.

## RESULTS

The mean age of mothers in GDM Group was 28.88 ± 3.11 years and in non-GDM Group was 27.74 ± 2.97 years(p=0.064). Majority of the mothers in GDM group (64%) as well as non GDM group (56%) were from the age group of 26-30 years. There was no statistically significant difference in terms of co-morbidities in both the groups.

In terms of mode of delivery, non GDM group had 56% spontaneous vaginal delivery compared to 14% in GDM Group(p=0.001), emergency lower segment caesarean section (LSCS) was 66% in GDM mothers compared to 32% in non-GDM(p=0.001) and vacuum delivery was 10% in GDM vs 0% in non GDM mothers (p=0.022) (Table1).

**Table1:Comparison between mothers with GDM and non GDM.**

| | | GDM | | Non-GDM | | p value |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| ***Maternal age (years)*** | 18-20 | 1 | 2% | 2 | 4% | 0.558 |
| | 21-25 | 4 | 8% | 9 | 18% | 0.137 |
| | 26-30 | 32 | 64% | 28 | 56% | 0.414 |
| | >30 | 13 | 26% | 10 | 20% | 0.640 |
| | Total | 50 | 100% | 50 | 100% | |
| | Mean ± SD | 28.88 ± 3.11 | | 27.74 ± 2.97 | | 0.064 |
| ***Maternal comorbidities*** | Hypothyroidism | 8 | 16% | 4 | 8% | >0.05 |
| | Hypertension | 4 | 8% | 2 | 4% | |
| | Polyhydramnios | 2 | 4% | 1 | 2% | |
| | Severe Preeclampsia | 2 | 4% | 1 | 2% | |
| | PIH | 1 | 2% | 2 | 4% | |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Mode of delivery*** | Spontaneous Vaginal | 7 | 14% | 28 | 56% | **0.001** |
| | Vacuum | 5 | 10% | 0 | 0% | **0.022** |
| | Elective LSCS | 5 | 10% | 6 | 12% | 0.749 |
| | Emergency LSCS | 33 | 66% | 16 | 32% | **0.001** |

There were 52% and 48% male neonates in GDM Group and Non-GDM group respectively while female neonates constituted 48% and 52% respectively(p>0.05).

The mean period of gestation was 37.14 ± 1.52 weeks in mothers with GDM and 38.21 ± 1.22 weeks in non GM group (0.001). In the non-GDM group, 84% of newborns were born between 37-40 weeks period of gestation in comparison to 52% in the GDM group(0.001). In the non-GDM group, 16 % of newborns were born with <37 weeks period of gestation in comparison to 48% in the GDM group(0.001).

In neonates born to non-GDM mothers, 24% were small for gestational age (SGA) compared to only 08% in mothers with GDM (p=0.029). In mothers with GDM, 88% neonates were appropriate for gestational age (AGA) compared to 76% in the non-GDM group(0.118).

In terms of neonatal morbidity, the incidence of prematurity and NICU admission were significantly higher in GDM group. The incidence of LBW (birth weight <2.5kgs), respiratory distress and tachypnea was comparable between both the groups. The incidence of Hyperbilirubinemia, Hypoglycemia and Polycythemia was significantly higher in GDM group as compared to Non-GDM Group (p<0.05). During the head to toe examination soon after birth, none of the neonates born to either GDM mothers or non-GDM mothers had any clinically detectable congenital malformations(Table 2).

**Table2: Comparison between neonates of mothers with GDM and non GDM.**

| | | GDM | | Non-GDM | | p value |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| ***Period of gestation*** | <37 weeks | 24 | 48% | 8 | 16% | **0.001** |
| | 37-40 weeks | 26 | 52% | 42 | 84% | **0.001** |
| | Mean ± SD | 37.14 ± 1.52 | | 38.21 ± 1.22 | | **0.001** |
| ***Gender*** | Male | 26 | 52% | 24 | 48% | >0.05 |
| | Female | 24 | 48% | 26 | 52% | |
| | Total | 50 | 100% | 50 | 100% | |
| ***Weight for gestational age*** | SGA | 4 | 08% | 12 | 24% | **0.029** |
| | AGA | 44 | 88% | 38 | 76% | 0.118 |
| | LGA | 2 | 4% | 0 | 0 | 0.153 |
| ***Neonatal Outcomes*** | NICU Admission | 14 | 28% | 4 | 8% | **<0.05** |
| | Low birth weight | 13 | 26% | 14 | 32% | >0.05 |
| | Prematurity | 24 | 48% | 8 | 16% | **<0.05** |
| | Respiratory distress | 1 | 2% | 0 | - | >0.05 |
| | Tachypnea | 1 | 2% | 0 | - | >0.05 |
| ***Neonatal Complications*** | Hyperbilirubinemia | 32 | 64% | 17 | 34% | **<0.05** |
| | Hypoglycemia | 8 | 16% | 1 | 2% | **<0.05** |
| | Polycythemia | 7 | 14% | 0 | - | **<0.05** |

LGA - Large for gestational age; AGA - Appropriate for gestational age; SGA - Small for gestational age; PIH – Pregnancy Induced Hypertension

The mean birth weight, length and Occipitofrontal Circumference (OFC) of neonates in GDM and Non-GDM Group did not have any statisticallly significant difference. The cord blood sugar values were significantly higher in GDM Group as compared to Non-GDM group (**p<0.05**). The other cord blood investigative values (Haemoglobin, Hematocrit, Platelet, Calcium and Bilirubin) were comparable between both the groups (p>0.05).

**Table 3: Comparison of Anthropometric and Biochemical parameters of Neonates.**

| | | GDM | | Non-GDM | | p value |
|---|---|---|---|---|---|---|
| | | Mean | SD | Mean | SD | |
| ***Anthropometry parameters*** | Weight (gms) | 2830 | 570 | 2850 | 490 | 0.844 |
| | Length (cm) | 46.94 | 2.80 | 47.24 | 1.99 | 0.538 |
| | OFC (cm) | 33.07 | 1.68 | 33.18 | 1.17 | 0.705 |
| ***Cord blood biochemical parameters*** | Haemoglobin (g/dL) | 16.12 | 1.81 | 15.72 | 1.24 | >0.05 |
| | Hematocrit (%) | 47.31 | 4.89 | 46.30 | 3.29 | >0.05 |
| | Platelet ($x10^3/\mu L$) | 241.9 | 0.62 | 240.3 | 0.66 | >0.05 |
| | Calcium (mg/dL) | 9.20 | 0.60 | 9.58 | 0.80 | >0.05 |
| | Bilirubin (mg/dL) | 1.57 | 0.60 | 1.44 | 0.84 | >0.05 |
| | Blood Sugar (mg/dL) | 79.64 | 30.41 | 67.10 | 19.22 | **<0.05** |

## DISCUSSION

A hospital based prospective case control study was conducted with 100 neonates to compare clinical outcomes and metabolic profiles in neonates of diabetic mothers compared to neonates of non-diabetic mothers.

In our country mortality and morbidity is still high among neonates born to diabetic mothers due to poor antenatal care, non-compliance to therapy, lack of awareness about the disease and its effects on fetus, non-booked deliveries and lack of adequate neonatal services. Metabolic complications are among the most important neonatal complications. In addition to being important contributors to early neonatal morbidity, the metabolic complications can lead to long term consequences. Early recognition and timely management can help reduce the severity and long term morbidity associated with these complications.[9,10]

The study sample was homogenous with no sigificant difference in the age/comorbidities other than GDM. The rate of spontaneous vaginal delivery (56% vs 14%) was significantly higher in non GDM group in current study. The incidence of LSCS(elective and emergency) was higher in mothers with GDM group (76% vs 44%) compared to non GDM group. This is consistent with various other studies conducted in other developing countries.[11,12] However, the significant observation in current study was that rate of emergency LSCS was significantly higher in the GDM group (66% vs 32%) while elective LSCS were comparable between two groups, thus eliminating the confounding factor of choice of patient. Thus emergency LSCS emerged as an independent complication for GDM mothers posing additional risks and warranting enhanced preparedness and extra resources in terms of healthcare infrastructure. The increased risk of emergency caesarean was consistent with a nation wide study in Denmark.[13]

Preterm births are an important cause of neonatal morbidity and mortality and the incidence of preterm births was significantly higher in mothers with GDM(48% vs 16%) in current study. This is in corroboration with study previous studies.[14] Majority (88%) of newborns in mothers with GDM were appropriate for gestational age (AGA) and only 04%(n=2) were large for gestational age (LGA). This is in contrast with multiple other studies which reported significantly higher weight for gestational age (30-40%) in mothers with GDM.[15,16,17] There are multiple hypotheses for accelerated weight gain in mothers with GDM and as per Pedersen, a sustained hyperglycaemia in utero leads to hyperinsulinemia with its consequential anabolic effects.[18] Studies have found a linear and continuous relationship between maternal glycemic levels, fetal insulin levels and body fat percentage.[19] However, in the current study, the mean neonatal birth weight was comparable in both the groups, none of the neonates had macrosomia and no congenital anomalies were observed during clinical head to toe examination at the time of birth. This is in contrast to study by Leandro et al on infants of diabetic mothers who reported incidence of major clinically detectable congenital malformations to be 3.12%. These major malformations were myelomeningocele, tracheo esophageal fistula & a cleft lip and palate.[20]

Among the anthropological prametres, the length and occipitofrontal circumference of neonates in GDM and Non-GDM Group were comparable (p>0.05). This could be explained on the basis of ours being a tertiary care armed forces hospital and all the pregnancies are registered in the early antenatal period. The patients follow structured diagnostic protocols, follow up and adhere to diet and treatment plans. They are meticulously screened by radiological and biochemical modalities for possible cogenital anomalies at the earliest. This observation also provides an indirect evidence that IDMs can have favourable outcomes with optimal glycemic control in mothers with GDM by implementing strict protocols.

Hyperbilirubinemia (64%) was the most common metabolic complication followed by hypoglycemia (16%) and polycythemia (14%) in newborns of GDM mothers (**p<0.05**) in the current study. This was consistent with multiple other studies thus giving strength to our existing knowledge and providing further impetus in implementing measures for stricter glycemic control during antenatal period.[21,22]

The cord blood biochemistry revealed significantly higher blood sugar values in the newborns of GDM mothers with consequent hypoglycemia in neonatal period. This is consistent with existing literature which reports a rapid decline in plasma glucose concentration of the neonates born to diabetic mothers. The proposed pathophysiology is that maternal hyperglycemia leads to fetal hyperglycemia, stimulating the fetal pancreas to synthesize excessive insulin. At the time of birth, due to the separation of the placenta, there is a sudden interruption of glucose infusion to the neonate but hyperinsulinemia persists leading to hypoglycemia.[9]

The other cord blood parametres (Haemoglobin, Hematocrit, Platelet, Calcium and Bilirubin) were comparable between both the groups ($p>0.05$).

The strength of the study is that a case control design in a homogenous population revealed significant feto-maternal complications in GDM pregnancies with potentially modifiable characteristics leading to favourable outcomes. The limitation in this study is that it is a single site hospital centric study with a relatively small sample size. Also, quantification of outcomes with different levels of maternal glycemic control was not done. A community-based study with a larger sample size is envisaged in future to further confirm our findings.

The study concludes that mothers with gestational diabetes are at increased risk for emergency caesaren section. The neonates of GDM mothers are at enhanced risk for prematurity, NICU admission, hyperbilirubinemia, hypoglycemia and polycythemia. However, unlike existing literature, it was shown that early diagnosis with strict monitoring and treatment protocols can reduce the other known complication of GDM, namely macrosomia and congenital anomalies. It is thus recommended that appropriate health authorities and policy makers should fervently implement measures for meticulous screening, diagnosis, and management of GDM at community level to reduce feto-maternal morbidity and mortality.

## CONCLUSION

The infants of diabetic mothers (IDM) had statistically significant higher percentage of preterm births, NICU admission, Hyperbilirubinemia, Hypoglycemia and Polycythemia. The anthropometric and cord blood parametres (Haemoglobin, Hematocrit, Platelet, Calcium and Bilirubin) were comparable in both the groups. GDM poses significant risks to both mother and neonate, however optimal glycemic control and meticulous monitoring and treatment protocols can reduce the incidence of certain known complications.

## CONFLICTS OF INTEREST

All authors have none to declare.

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